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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/802,574	03/17/2004	James J. Schmidt	003/289/SAP	3751

7590 11/12/2004

ATTN: MCMR-JA (Elizabeth Arwine- PATENT ATTY)
U.S. Army Medical Research and Material Command
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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 11/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/802,574	SCHMIDT ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) *2,3,6-15,17,19,21,22,25-38,40 and 42-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,16,18,20,23,24,39 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/17/24*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II, claims 1, 4, 5, 16, 18, 20, 23, 24, 39 and 41, and botulinum toxin B, and a kit containing the peptide substrate in the response filed August 31, 2004 is acknowledged. The traversal is on the ground(s) that the instant application is a continuation of an allowed application (09/962,360), where the claims drawn to substrates of botulinum toxin serotype A (4 substrates) are examined, and examination of the substrates of all the remaining neurotoxins, i.e., B, F, D and E (a total of 7 substrates) would not place undue burden on the Examiner. This is not found persuasive because each peptide substrate requires amino acid sequence search against 6 databases, and there are 3 substrates (SEQ ID NOs: 3, 4 and 9) for botulinum toxin B and tetanus toxin, and 6 substrates (SEQ ID NOs: 5, 6, 7, 10, 11 and 12) for botulinum toxin D, E and F, thus a total of 54 (9 x 6) data sets need to be searched and analyzed, if botulinum toxins D, E and F were included. Therefore, search and examination of the substrates (9 substrates) for all the remaining neurotoxins would place undue search burden on the Examiner. Thus, claims 1, 4, 5, 16, 18, 20, 23, 24, 39 and 41, and SEQ ID NOs: 3, 4 and 9 are examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 4, 16, 20, 23 and 39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a specific fluorescence resonance energy transfer

(FRET) peptide substrate (e.g., SEQ ID NO: 3 or 4) or a specific fluorescent peptide substrate (e.g., SEQ ID NO: 9) attached to multi-well plates for a specific clostridial neurotoxin such as botulinum toxin B or tetanus toxin, where the amino acid sequence, the fluorescent group and fluorescence quenching group in the sequence are defined; and a kit containing the FRET or the fluorescent peptide substrate; or specific peptide substrates attached to the microtitre plate for botulinum toxins A, B and Tetanus toxin as indicated in the prior art, does not reasonably provide enablement for a clostridal neurotoxin peptide substrate having a signal moiety and a signal quenching moiety, or a botulinum toxin peptide substrate being modified to attach to a solid material; and a kit containing the peptide substrate, where the amino acid sequence, the signal moiety and the signal quenching moiety of the peptide substrates are not defined. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1, 4, 16, 20, 23 and 39 encompass a clostridal neurotoxin peptide substrate having a signal moiety on one side of the cleavage site and a signal quenching moiety on the other side of the cleavage site (claims 1 and 4); a botulinum toxin peptide substrate being modified to attach to a solid material (claims 20 and 23); and a kit containing the peptide substrate (claims 16 and 39). The specification, however, only discloses cursory conclusions (page 6, line 16-page 7, line 9) without data supporting the findings, which state that the invention provides clostridial neurotoxin peptide substrate for use in FRET assays and solid phase assays, and a method for detecting the presence of clostridial neurotoxins in samples based on the proteolytic activities of the toxins. There are no indicia that the present application enables the full scope of the claimed

invention in view of the modified peptide substrate of clostridial neurotoxins as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence or absence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the clostridial neurotoxin peptide substrates having a signal moiety and a signal quenching moiety and botulinum toxin peptide substrates being modified to attach to a solid material, which are not adequately described or demonstrated in the specification.

(2). The presence or absence of working examples:

There are no working examples indicating the variants except for specific FRET peptide substrates (e.g., SEQ ID NO:3 or 4 for botulinum toxin B or tetanus toxin), and specific fluorescent peptide substrates (e. g., SEQ ID NO:9) which are modified to attach to multi-well plates for botulinum toxin A, B, D, F (Examples 1 and 2).

(3). The state of the prior art and relative skill of those in the art:

The prior art (Shone *et al.* (WO 95/33850) teach a peptide substrate of VAMP, SNAP-25 or Syntaxin attached to a solid phase is used in botulinum toxin assay; Anne et al. (Anal. Biochem 291, 253-261, (2001), post priority date reference) describe a specific FRET substrate

for botulinum toxin B. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identities of modified clostridial neurotoxin peptide substrates containing various signal moieties and signal quenching moieties, and of botulinum toxin peptide substrates which have been modified to attach to a solid material, and on the activities of these peptide substrates.

(4). Predictability or unpredictability of the art:

The specification indicates the concept of FRET assays have been known for many proteases, however, the knowledge provided by FRET assays for other proteases cannot be applied directly to the development to FRET substrates for clostridial neurotoxin protease activity due to their extreme substrate specificities, sensitivities to even minor structural changes in substrates, and the very large substrate recognition requirements for these toxins (page 3, lines 25-35; page 14, lines 3-15). Thus, the activity of clostridial neurotoxin peptide substrate which has been modified to contain a signal moiety and a signal quenching moiety or to attach to the plate is highly unpredictable, if the sequence, the signal moiety and signal quenching moiety of the peptide substrates are not defined.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a clostridal neurotoxin peptide substrate having a signal moiety and a signal quenching moiety; a botulinum toxin peptide substrate being modified to attach to a solid material; and a kit containing the peptide substrate. The specification indicates specific FRET peptide substrates (e.g., SEQ ID NOs:3 and 4) for botulinum toxin B and specific fluorescent peptide substrates (e.g., SEQ ID NO:9) which are modified to attach to multi-well

plates for botulinum toxins A, B, D and F (Examples 1 and 2). However, the specification has not indicated the introduction of various signal moieties and signal quenching moieties into various peptide sequences except for specific FRET peptide substrates, nor has demonstrated various peptide substrates being modified to attach to solid phase except for specific immobilized peptide substrates. Furthermore, the specification has not demonstrated the substrate activities of various modified peptide substrates and the use of these peptide substrates in assays. There are no working examples indicating the claimed variants except for specific FRET substrates for a botulinum toxin, and specific fluorescent substrate for botulinum toxins A, B, D and F. Since the specification fails to provide sufficient teachings on the identities and activities of various modified clostridial neurotoxin substrates, it is necessary to have additional guidance on the identities of various signal moieties and signal quenching moieties and various sequences of peptide substrates and to carry out further experimentation to assess the activities of these peptide substrates, the experimentation is undue because further research is required to identify active substrates for botulinum toxin B or tetanus toxin.

(6). Nature of the Invention

The scope of the claim includes a clostridal neurotoxin peptide substrate having a signal moiety and a signal quenching moiety, and a botulinum toxin peptide substrate being modified to attach to a solid material, however the specification has not demonstrated the make/use of various clostridal neurotoxin peptide substrates. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, the teachings in the specification are limited, and the activity

of the modified peptide substrate is unpredictable, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the activities of various modified clostridal neurotoxin peptide substrates.

3. Claims 1, 4, 16, 20, 23 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 4, 16, 20, 23 and 39 are directed to a clostridal neurotoxin peptide substrate having a signal moiety and a signal quenching moiety; a botulinum toxin peptide substrate being modified to attach to a solid material; and a kit containing the peptide substrate. While the specification indicates that the invention provides clostridial neurotoxin peptide substrate for use in FRET assays and solid phase assays, and a method for detecting the presence of clostridial neurotoxins in samples based on the proteolytic activities of the toxins, the specification does not disclose a genus of variants for a clostridal neurotoxin peptide substrate having a signal moiety and a signal quenching moiety; and a botulinum toxin peptide substrate modified to attach to a solid material.

The specification discloses specific FRET peptide substrates (e.g., SEQ ID NOs:3 and 4) for botulinum toxin B and specific fluorescent peptide substrates (e.g., SEQ ID NO:9) modified to attach to multi-well plates (Examples 1 and 2). However, the specification does not describe a genus of variants for a clostridal neurotoxin peptide substrate having a signal moiety and a signal quenching moiety; and a botulinum toxin peptide substrate modified to attach to a solid material.

A description of specific botulinum toxin substrates (e.g., SEQ ID NOs: 3, 4 and 9) does not provide original descriptive support for signal quenching and immobilized peptide substrates of a clostridial neurotoxin. The disclosure of specific FRET and immobilized peptide substrates for a specific botulinum toxin does not meet the written description provision of 35 USC 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Applicants have described specific FRET and immobilized peptide substrates for a specific clostridial neurotoxin such as botulinum toxin B, however, a genus of variants for a signal quenching clostridal neurotoxin peptide substrate and an immobilized botulinum toxin peptide substrate have not been sufficiently described nor disclosed.

The skilled artisan cannot envision all the contemplated signal quenching and immobilized peptide substrates for a clostridial neurotoxin based upon the general suggestion of a functional characteristic of the peptides. The detailed sequences of peptide substrates must be taught, therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of preparation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what

one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF'S were found unpatentable due to lack of written description for the broad class.

Therefore, only those embodiments described and disclosed meet the written description requirement and not the full breadth of the claim meets the written description provision of 35 USC 1 12, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 4, 5, 16, 18, 20, 23, 24, 39 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, 4, 5, 16, 18, 20, 23, 24, 39 and 41 are indefinite because of the use of the term "have been modified", "a signal moiety" or "a moiety". The term "have been modified", "a signal moiety" or "a moiety" renders the claim indefinite, it is unclear how and where the peptide substrates have been modified, and what structure the signal moiety or the signal quenching moiety refers to. Claims 4, 5, 16, 18, 23, 24, 39 and 41 are included in this rejection for being

dependent on a rejected claim and not correcting the deficiency of the claim from which it depends.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 20 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Shone *et al.* (WO 95/33850).

Shone *et al* teach a peptide substrate of VAMP, SNAP-25 or Syntaxin attached to a solid phase is used in a botulinum toxin assay (page 10, paragraph 3). For example, a peptide having the sequence of VAMP isoform-1, residues 60-94 plus an C-terminal Cys, which is attached to microtitre plate, is used as the substrate for botulinum toxin B, and after cleavage, the C-terminal segment remains attached to the plate (Example 1, Fig. 1; claims 20 and 23); a solid phase peptide of VAMP isoform-1, residues 33-94 is used for assay tetanus toxin; and a solid phase peptide taken from SNAP-25, residues 137-206 is used for assay botulinum toxin A.

Conclusion

6. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CMK
November 9, 2004